Application No. 10/542,043

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Amendment under 37 C.F.R. 1.116 dated October 21, 2008

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Listing of the Claims:

This listing of claims will replace all prior version, and listings, of claims in the application.

- (Currently amended) A method for determining a haplotype comprising at least three polymorphic markers that are about one or more kilo base pairs apart of a subject comprising the steps of:
 - diluting a nucleic acid sample from the subject to determine the haplotype of the at least three polymorphic markers that are about one or more kilo base pairs apart into a single nucleic acid molecule dilution;
 - (b) amplifying the single nucleic acid molecule dilution with at least a first, a second and a third primer pair, wherein each primer pair flanks a nucleic acid region that is about 100bp long and wherein the at least first, the second and the third primer pair each are designed to amplify a different nucleic acid region designated as a first, a second and a third nucleic acid region, wherein the at least the first, the second, and the third nucleic acid region each comprise at least one polymorphic site designated as a first, a second and a third polymorphic site, wherein the first, the second and the third polymorphic site are one or more kilobase pairs apart;
 - (c) genotyping the polymorphic site in the at least the first nucleic acid region, [[and]] the second nucleic acid region and the third nucleic acid region thereby resulting in at least a first, a second and a third genotype; and
 - (d) determining the haplotype comprising polymorphic markers about one or more kilo base pairs apart from the at least the first, the second and the third genotype to obtain a haplotype for the subject.
- (Previously presented) The method of claim 1, further comprising repeating steps a-c at least three times from the nucleic acid sample to obtain at least four genotype replicas from the subject and thereafter subjecting the at least four genotype replicas to a statistical analysis to determine the haplotype.
- (Original) The method of claim 2, further comprising comparing the haplotype with a
 haplotype from a control or a database of haplotypes from controls to determine
 association of the haplotype with a biological trait.

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- (Currently amended) The method of claim 1, wherein the polymorphic markers [[is]] are
 [[a]] single nucleotide polymorphisms.
- (Currently amended) The method of claim 1, wherein the polymorphism polymorphic markers [[isi]] are [[a]] deletions, [[an]] insertions, [[a]] substitutions or [[an]] inversions.
- 6. (Currently amended) The method of claim 1, wherein the polymorphism polymorphic markers [[is]] are a combination of one or more markers selected from the group consisting of [[a]] single nucleotide polymorphisms, deletion, [[an]] insertions, [[a]] substitutions or [[an]] inversions.
- (Previously presented) The method of claim 1, wherein genotyping is performed using primer extension and mass spectrometric detection.
- 8. (Original) The method of claim 2, wherein 12-18 genotype replicas are produced.
- (Currently amended) A method of diagnosing a disease condition or disease susceptibility by determining a disease related haplotype comprising at least three polymorphic markers that are one or more kilo base pairs apart in a subject comprising the steps of:
 - diluting a nucleic acid sample from the subject into a single nucleic acid molecule dilution;
 - (b) amplifying the single nucleic acid molecule dilution with at least a first, a second and a third primer pair, wherein each primer pair flanks a nucleic acid region of about 100bp long and wherein the at least first, the second and the third primer pair each is designed to amplify a different region designated as a first, a second and a third nucleic acid region wherein each nucleic acid region comprises at least one polymorphic marker in the nucleic acid template;
 - genotyping the polymorphic site in the at least the first, the second and the third nucleic acid region thereby resulting in at least a first, a second and a third genotype;
 - (d) determining the haplotype of the subject from the at least first, the second and the third genotype; and
 - (e) comparing a haplotype of the subject to known disease-associated haplotypes, wherein a match in the haplotype of the subject with any one of the known

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disease-associated haplotypes indicates that the subject has the disease or that the subject is susceptible for the disease,

- 10. (Previously presented) The method of claim 9, further comprising repeating steps a c at least three times from the nucleic acid sample to obtain at least four genotype replicas from the subject and thereafter subjecting the at least four genotype replicas to a statistical analysis to determine the haplotype.
- 11. (Original) The method of claim 10, wherein 12-18 replicas are produced.
- 12. (Currently amended) A method of determining a haplotype comprising at least three polymorphic markers that are about one or more kilo base pairs apart of a subject comprising the steps of:
 - (a) treating a nucleic acid sample from the subject with a composition that differentially affects an epigenetically modified nucleotide in the nucleic acid sample to effectively create at least a first, a second and a third polymorphic marker into the nucleic acid sample based on each epigenetically modified nucleotide;
 - (b) diluting the nucleic acid sample of step (a) into a single nucleic acid copy dilution:
 - (c) amplifying the single nucleic acid copy dilution using at least a first, a second and a third different primer pair, wherein each primer pair flanks a nucleic acid region of about 100 bp long and wherein the first, the second and the third primer pair each amplify a different nucleic acid region designated as a first, a second and a third nucleic acid region, wherein the first, the second and the third nucleic acid region each comprise at least one polymorphism based on the epigenetically modified nucleotide, and wherein the at least first, the second and the third polymorphic site are about one or more kilo base pairs apart;
 - (d) genotyping the amplified sample resulting in at least a first, a second and a third genotype; and
 - determining the haplotype of the subject from the at least first, the second and the third genotype.

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- 13. (Previously presented) The method of claim 12, further comprising repeating the steps bd at least three times to obtain at least four genotype replicas from the subject and thereafter determining a haplotype of the subject based on the genotype replicas by subjecting the at least four genotype replicas to a statistical analysis.
- 14. (Original) The method of claim 13, wherein 12-18 replicas are produced.
- (Original) The method of claim 12, wherein the epigenetically modified nucleotide is a methylated nucleotide.
- (Original) The method of claim 15, wherein the nucleic acid sample is treated with bisulfite.
- 17. (Currently amended) A method of determining a haplotype comprising at least one methylated nucleotide that are one or more kilo base pairs apart in a subject comprising the steps of:
 - digesting a nucleic acid sample from the subject with a methylation-sensitive restriction enzyme so that either unmethylated DNA or methylated DNA is left intact, depending on which enzyme is used;
 - (b) diluting the digested nucleic acid sample of step (a) into a single nucleic acid molecule dilution;
 - (c) amplifying the single nucleic acid molecule dilution with at least a first, a second and a third primer pair, wherein each primer pair flanks a nucleic acid region of about 100 bp long and wherein the first, the second and the third primer pair each amplify a different nucleic acid region designated as a first, a second and a third nucleic acid region, wherein the first, the second and the third nucleic acid region each comprise at least one polymorphic marker of which at least one is a result of a methylated nucleic acid, and wherein the at least first, the second and the third polymorphic marker are one or more kilo base pairs apart;
 - genotyping the amplified samples in the at least first nucleic acid region and the second nucleic acid region thereby resulting in at least a first and a second genotype; and

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- determining a haplotype of a methylated nucleic acid wherein at least one polymorphic marker next to a methylation site, together with the methylation site, constitutes a haplotype.
- 18. (Previously presented) The method of claim 17, further comprising repeating the steps bf at least three times to obtain at least four genotype replicas from the subject and thereafter determining a haplotype of the subject based on the genotype replicas by subjecting the at least four genotype replicas to a statistical analysis.
- (Previously presented) The method of claim 1, wherein at least 5 primer pairs amplifying at least five different nucleic acid regions are used.
- (Previously presented) The method of claim 1, wherein at least 10 primer pairs amplifying at least 10 different nucleic acid regions are used.
- 21. (Previously presented) The method of claim 1, wherein the at least one polymorphic site in the first nucleic acid region is three or more kilo base pairs apart from the at least one polymorphic site in the second nucleic acid region.
- 22. (Previously presented) The method of claim 1, wherein the at least one polymorphic site in the first nucleic acid region is four or more kilo base pairs apart from the at least one polymorphic site in the second nucleic acid region.
- 23. (Previously presented) The method of claim 1, wherein the at least one polymorphic site in the first nucleic acid region is 15-20 kilo base pairs apart from the at least one polymorphic site in the second nucleic acid region.
- 24. (Cancelled)